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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,778	08/09/2001	Deborah Dee Jaworski	GM50074	9516

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SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER
WEBER, JON P

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/07/2003 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/925,778	JAWORSKI ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

Claims 1-20 have been presented for examination.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-11 in Paper No. 10, filed 19 February 2003 is acknowledged. The traversal is on the ground(s) that the search terms are shared between the groups. This is not found persuasive because search burden was established by separate classification in the Office action of 11 October 2002.

The requirement is still deemed proper and is therefore made FINAL. Claims 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10. It is suggested to cancel the non-elected claims in response to this Office action to expedite prosecution.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 22. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 asserts that manganese is used as a substrate by DXR. In actuality, manganese is a cofactor, not a substrate. This use of substrate is contrary to art-accepted usage.

Claim 2 recites "binding of DXR with a cellular component" which is vague and indefinite because the nature and manner of the cellular component bound is unclear.

Claim 6 (i) and (ii) recite "an polypeptide" which is grammatically unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeidler et al. (1998), Kuzuyama et al. (1998), Jomaa et al. (1999), Jomaa (WO 00/41473) [the English language equivalent, CA 2,360,366 will be referenced] and Grolle (2000) in view of Takahashi et al. (1998), Croteau et al. (US 6,281,017) and Sicard et al. (2000).

Zeidler et al. (1998) disclose that fosmidomycin inhibits DXP reductoisomerase from plants. Zeidler et al. (1998) lacks inhibiting DXP reductoisomerase from *Haemophilus influenzae*.

Kuzuyama et al. (1998) disclose that fosmidomycin and its analogs FR-33289 and FR-900098 inhibit DXP reductoisomerase from *E. coli*. Fosmidomycin has a potent antibacterial activity against most Gram-positive and some Gram-negative bacteria (page 7914). DXP reductoisomerase is suggested to be a new molecular target for chemotherapeutically useful drugs (page 7916). Kuzuyama et al. (1998) lack inhibiting DXP reductoisomerase from *Haemophilus influenzae*.

Jomaa et al. (1999) disclose that DXP reductoisomerase from *Plasmodium falciparum* was inhibited by fosmidomycin and its derivative, FR-900098. The DOXP pathway is absent in mammals and fosmidomycin and FR-900098 are known to have low toxicity (page 1574). The efficacy of these drugs against multidrug-resistant parasites and their low manufacturing costs and high stability make them very attractive as a potential new class of antimalarial drugs (page 1575). Jomaa et al. (1999) lack inhibiting DXP reductoisomerase from *Haemophilus influenzae*.

Jomaa (WO 00/41473) disclose that 3-isoxazolidinones and hydroxylamic acids have therapeutic activity against a wide range of bacteria, fungi and parasites (in particular the genus

Haemophilus, page 11) because they inhibit 1-deoxy-D-xyulose 5-phosphate (DOXP) reductoisomerase (EC 1.1.1.267), an enzyme in a pathway that has not been detected in humans (page 17). Example 1 demonstrates the inhibition of DOXP reductoisomerase, while example 2 demonstrates antimalarial activity. Jomaa (WO 00/41473) lack explicit inhibiting DXP reductoisomerase from *Haemophilus influenzae.*

Grolle (2000) disclose that fosmidomycin inhibits DXP reductoisomerase from *Zymomonas mobilis*. Grolle (2000) lacks inhibiting DXP reductoisomerase from *Haemophilus influenzae.* (See Rohmer et al, 1996, for information re the pathway from this organism.)

Takahashi et al. (1998) disclose that the DXP reductoisomerase from *E. coli* shows significant homologies to hypothetical protein of unknown function from several organisms including *Haemophilus influenzae* (Abstract; Fig. 4, Gen Bank Acc. No. P44055).

Croteau et al. (US 6,281,017) in the references cited indicates that in GenBank Accession NO. U32763, the nucleic acid sequence of a portion of the *Haemophilus influenzae* genome includes a sequence that encodes a putative DXP reductoisomerase.

Sicard et al. (2000) disclose that metabolic routes are good chemotherapeutic targets for discriminating between host and parasite. The nonmevalonate DXP pathway is identified as a most suitable target. The DXP reductoisomerase is said to be highly conserved in evolution.

A person of ordinary skill in the art at the time the invention was made would have been motivated to inhibit DXP reductoisomerase from *Haemophilus influenzae* with e.g. fosmidomycin according to the methods of Zeidler et al. (1998), Kuzuyama et al. (1998), Jomaa et al. (1999), Jomaa CA 2,360,366 and Grolle (2000) because these all demonstrate that this enzyme can be inhibited from a variety of organisms and that inhibiting this enzyme kills the

target bacteria and parasites without posing a danger to mammalian hosts who lack this enzyme. Jomaa CA 2,360,366 explicitly suggests that DXR reductoismerase from *Haemophilus influenzae* is expected to be inhibited, while Kuzuyama et al. (1998) indicate that a wide range of Gram-positive and some Gram-negative bacteria are sensitive to the DXR reductoisomerase inhibitor, fosmidomycin and its analogs. Finally, Takahashi et al. (1998) and Croteau et al. (US 6,281,017) clearly indicate that DXR reductisomerase is structurally similar (homologous sequence) to the *E. coli* enzyme, and Sicard (2000) states that DXR reductoisomerase is highly conserved in evolution and makes a good therapeutic target.

It can be seen from the cited references that compounds that inhibit DXR reductoisomerase from one organism inhibit the same enzyme from organisms differing as much as plants and bacteria and entirely different genera of bacteria. Several references remarked on the importance of developing inhibitors of this enzyme for chemotherapeutics against bacteria and parasites like malaria. The enzyme *Haemophilus influenzae* is specifically suggested as a target for fosmidomycin. The gene for the enzyme from *Haemophilus influenzae* has been disclosed in a couple of GenBank deposits, albeit with the function of the protein unknown at the time of deposit. Nevertheless, Takahashi et al. recognized the sequence as being DXP reductoisomerase from *Haemophilus influenzae.*

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to inhibit DXP reductoisomerase from *Haemophilus influenzae.*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
May 1, 2003